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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,069	03/30/2001	Kenneth T. Wheeler	9151-6	8239

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,069	WHEELER ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *8-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11/13/02 7/10/01
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Response to Restriction Requirement filed 11/3/03 has been entered

2. Applicant's election with traverse of Group II (Claims 1-7 and 11, on 11/3/03, is acknowledged. The traversal is on the ground(s) that the search of Groups I, III, IV, VI, IX and XI would overlap with the search of Group II and would not cause an undue burden on the Examiner. Applicant's arguments have been fully considered but not found persuasive. A search of Groups II and I, III, IV, VI, IX and XI would not be co-extensive particularly with regard to the literature search. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner. Claims 8-10,12-32 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Drawings filed 7/20/01 are approved by the Examiner.

4. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Figures 3 and 5 contain sequences which have not been identified by SEQ ID NO:. All sequences in Figure 2 and 5 must be identified by their corresponding SEQ ID NO:. Correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 7, 11 are indefinite because the name $\sigma 1\beta$ receptor does sufficiently define the claimed receptor and does not provide any structural and functional limitations so as to allow the metes and bounds of the claim to be determined. It is suggested, to overcome the rejection, receptor be identified by SEQ ID NO.

Claim 1 is indefinite because "stringent conditions" of hybridization are not specified. It is not clear what are the "stringent conditions". The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claim cannot be determined without the disclosure of said conditions.

Claims 3-6 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 and 11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A "specific utility" is a utility that is specific to the subject matter claimed, as opposed to a "general utility" that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well

established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A "well established utility" must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 1-7 and 11. The invention is directed to an isolated nucleic acid molecule (encoding $\sigma 1\beta$ receptor) comprising: a) nucleic acid molecule encoding a polypeptide having the nucleotide sequence of SEQ ID NO:1 or degenerate variants thereof, b) nucleic acid molecule which hybridizes under stringent conditions to the nucleic acid molecule of a or degenerate variants thereof, c) nucleic acid molecule encoding a the polypeptide disclosed in SEQ ID NO:2, e) vector comprising the nucleic acid of claim 1 and cell comprising said vector, f) method for producing a protein comprising the amino acid sequence of SEQ ID NO:2 or comprising fragments thereof.

The specification discloses the $\sigma 1\beta$ receptor of SEQ ID NO:2 is encoded by the polynucleotide of SEQ ID NO:1. Mach et al (see IDS, Cancer Research Vol. 57, 1546-161, 1997) disclose, although the expression of $\sigma 1$ and $\sigma 2$ receptors is heterogeneous their function is unknown (see Abstract). Malliga et al (see IDS, The Journal of pharmacological and Experimental Therapeutics, Vol. 289, page 251-260) disclose the biochemical and pharmacological profiles of these receptors differ markedly, indicating species and cell type dependent differential expression of various subtypes of σ receptors in immune cells. (see

page 252, column 1, first paragraph). Further WO 97/34792 (see IDS) also discloses the function of $\sigma 2$ is unknown (see page 1). The $\sigma 1\beta$ receptor of instant invention is expressed in a wide variety of tissues, normal and cancerous. Therefore based on the art and the disclosure the functionality of claimed $\sigma 1\beta$ receptor of SEQ ID NO:2 is unknown. Members of the $\sigma 1$ receptor family are also highly divergent in their effects and ligand specificity. Based on the homology data to $\sigma 1$ receptor family and the general classification into the superfamily of $\sigma 1$ receptor family, the specification discloses the claimed $\sigma 1\beta$ receptor is useful for detecting, preventing and/or treating diseases associated with cancer. There is no clear nexus between the treatable diseases/disorders and use of claimed $\sigma 1\beta$ receptor. In light of the specification the skilled artisan can not come to any conclusions as to the function of claimed nucleic acid encoding the $\sigma 1\beta$ receptor of SEQ ID NO:2 or variants thereof.

The utility of claimed protein cannot be implicated solely from homology to the proteins known in the art because the art does not provide teaching stating that all protein disclosed have the same activity, same effects, the same ligands and are involved in the same disease states. In light of the specification and art the skilled artisan can not come to any conclusions as to the function of protein encoded by claimed nucleic acid. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO:2 possesses, or how to specifically assay for such, ligands that bind, promoters that activate; nor are any cell types/tissues disclosed that specifically nor are any disease states disclosed that are directly related to said protein dysfunction.

The specification fails to disclose, what disease is associated with claimed $\sigma 1\beta$ receptor dysfunction or what drugs affect a specific claimed receptor function. The claimed $\sigma 1\beta$ receptor may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its endogenous ligand characterized and functionality determined. The inclusion in the family of σ receptor does not constitute either a specific and substantial asserted utility or a well established utility for that particular $\sigma 1\beta$ receptor. This is analogous to all proteins/nucleic acid of σ receptor can be used as markers on a gel.

Specification discloses claimed receptors are useful in screening but the specification does not disclose what claimed $\sigma 1\beta$ receptor specifically regulates and what specific disease, claimed $\sigma 1\beta$ receptor, is a target for. What would be the use of using the claimed $\sigma 1\beta$ receptor on a panel for drug screening. Further the functional effects of ligand binding may remain uncertain even after extensive experimentation. The ordinary artisan can only speculate on the utility for the ligand for $\sigma 1\beta$ receptor. A utility to orphan $\sigma 1\beta$ receptor cannot be assigned without knowledge of what disease is associated with claimed $\sigma 1\beta$ receptor dysfunction or what drugs/ligands effect a specific claimed $\sigma 1\beta$ receptor function. The superfamily of σ receptor is highly divergent in their effects and compound specificity. The utility of claimed $\sigma 1\beta$ receptor cannot be implicated solely from homology to known $\sigma 1$ receptors or their protein domains because the art does not provide teaching stating that all members of family of $\sigma 1$ receptors must have

the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary.

It can be argued the claimed $\sigma 1\beta$ receptor are useful as tools as reagents and targets as a molecular target in the diagnosis and treatment of claimed $\sigma 1\beta$ receptor mediated disorders. All members of the $\sigma 1$ receptor family have a utility in selectively screening of candidate drugs that target $\sigma 1$ receptors. However, for a utility to be "well-established" it must be specific, substantial. In this case, as all $\sigma 1$ receptors are in some combination useful in selectively screening of candidate drugs that target $\sigma 1$ receptors and in toxicology testing. However, the particulars of screening of candidate drugs, that target claimed $\sigma 1\beta$ receptor and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:1 and 2. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed $\sigma 1\beta$ receptor is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the $\sigma 1\beta$ receptor family. Again, this is a utility which would apply to virtually ever

member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants' individual $\sigma 1\beta$ receptor is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using $\sigma 1\beta$ receptor has no "well-established" use. The artisan is required to perform further experimentation on the claimed $\sigma 1\beta$ receptor itself in order to determine to what "use" any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed $\sigma 1\beta$ receptor and a disease or disorder. The presence of claimed $\sigma 1\beta$ receptor in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed $\sigma 1\beta$ receptor and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed $\sigma 1\beta$ receptor to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed $\sigma 1\beta$ receptor is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for

use of claimed $\sigma 1\beta$ receptor as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed $\sigma 1\beta$ receptor and any disease or disorder and the lack of any correlation between the claimed $\sigma 1\beta$ receptor with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Further, $\sigma 1$ receptor family belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific and utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the $\sigma 1$ receptor family has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological

activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed $\sigma 1\beta$ receptor, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a "real world" manner based on the diversity of biological activities possessed by the $\sigma 1$ receptor family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ

1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide encoded by the nucleic acid of SEQ ID NO:1 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1. Applicant has failed with respect to claimed $\sigma 1\beta$ receptor, has not described the family of $\sigma 1$ receptors in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:2 or the polynucleotide of SEQ ID NO:1 or variants thereof has any substantial use. The record shows that the family of proteins having $\sigma 1$ receptor domains is diverse), and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven

effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed $\sigma 1\beta$ receptor might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The rejection under § 101 follows *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class.

Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed $\sigma 1\beta$ receptor (TMP) has no utility, methods of its use are also rejected for lack of utility.

7. Claims 1-7 and 11 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed $\sigma 1\beta$ receptor polynucleotide (SEQ ID NO:1) encoding the polypeptide of SEQ ID NO:2, variants thereof. Further experimentation is necessary to attribute a utility to the claimed nucleic acid encoding $\sigma 1\beta$ receptor and variants thereof.

The claims fail to disclose how to use the claimed invention for the reasons given above (lack of utility). Further the claims are drawn to an orphan $\sigma 1\beta$ receptor. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed $\sigma 1\beta$ receptor. Therefore nucleic acid encoding unrelated and inactive proteins are encompassed by the claims. The

specification does not disclose how to produce active variants or how to use inactive ones. Substitutions that result in active variants are not disclosed. Substitutions that are detrimental to $\sigma 1\beta$ receptor variant activity are not disclosed. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Further, many of the polypeptides, encoded by the nucleic acids which hybridize to the polynucleotide encoding the claimed $\sigma 1\beta$ receptor, may be inactive or unrelated to the nucleic acid encoding the polypeptide of SEQ ID NO:2. Further many of the nucleic acids encoding variants of $\sigma 1\beta$ receptor encompassed by the claims may be inactive or unrelated to the nucleic acid of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2. The specification does not disclose how to produce active variants. The specification does not disclose a utility for or how to use said inactive or unrelated polypeptides encoded by claimed nucleic acid molecule. The claimed nucleic acid encodes an $\sigma 1\beta$ receptor whose functionality have not been disclosed. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed $\sigma 1\beta$ receptor. There is no disclosure of how to assay variants identified by the hybridization procedure, or even the variant of $\sigma 1\beta$ receptor, since the natural ligand, compound transported and function of the claimed invention is unknown. Specific stringent hybridization conditions have not been provided.

Therefore the hybridization conditions recited in the claim do not constitute a meaningful structural limitation.

Pertaining to claim 1, instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to any nucleic acid hybridizing to same, given the lack of guidance regarding what sequences would hybridize specifically to polynucleotide of SEQ ID NO:1) and not other, related sequences. Further, many of the polypeptides encoded by the nucleic acids isolated by hybridization will be unrelated to the protein of instant invention, being devoid of its characteristic structural and functional features. Said unrelated polypeptides may be produced by frame shift

in the coding sequence of the nucleotide, for example. Other polypeptides may be truncated, for example. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:2 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

Furthermore, the specification does not reasonably provide enablement for the scope of use of nucleic acid encoding polypeptides comprising variants to the polypeptide of SEQ ID NO:2, or comprising nucleic acid variants to the nucleic acid of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not teach how to make functional claimed receptor variants or to use inactive variants. The prior art teaches that amino acid substitutions produce unpredictable results in a structurally related protein. Furthermore, neither the specification nor the prior art provide any guidance as to which amino acids could be altered, nor does the specification provide any guidance as to how the skilled artisan could use inactive claimed $\sigma 1\beta$ receptor variants. Therefore, it would require undue experimentation to practice this

invention as claimed, because the skilled artisan would have no reasonable expectation that claimed $\sigma 1\beta$ receptor variants could be used for any purpose. Further the nucleic acids that comprise variants of SEQ ID NO:1 or encode variants of the polypeptide of SEQ ID NO:2 may not specifically hybridize to the polynucleotide of SEQ ID NO:1 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:2. Applicant has not disclosed how to use said nucleic acids that do not specifically hybridize the polynucleotide of SEQ ID NO:1 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:2. Further the specification does not disclose how to use nucleic acids that comprise variants of SEQ ID NO:1 or encode fragments or variants of the polypeptide of SEQ ID NO:2 without functional activity.

Therefore, pertaining to claimed variants, due to the large quantity of experimentation necessary to identify the nucleic acids encoding polypeptides with the structural and functional features of instant $\sigma 1\beta$ receptor (the critical feature of the invention is not disclosed, i.e. structure and function relationship), the lack of direction/guidance presented in the specification regarding the identification, purification, isolation, characterization and assaying (no specific assay disclosed which measures claimed $\sigma 1\beta$ receptor activity) of claimed invention, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:1 and 2 are also encompassed by the claim), construction of active variants (no disclosure of which amino acids can be mutated and still provide active protein) and the breadth of the claim which fail to recite structural (except for the nucleic acid of

SEQ ID NO:1, encoding the polypeptide of SEQ ID NO:2) and functional limitations containing critical feature of the invention, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope. For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention. As is evidence in the discussions *supra*, each of these factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to use the instant invention. Further since the claimed $\sigma 1\beta$ receptor has no utility, vector comprising the claimed nucleic acid, cell comprising said vector, composition comprising claimed nucleic acid, kit comprising said composition and method of producing polypeptide encoded by claimed nucleic also rejected under 35 USC § 112, 1st paragraph

Claim Rejection 35 USC § 112, 1st paragraph (Written Description)

7. Claims 1, 2, 5-7 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are claims 1, 2, 5-7 and 11 are directed to an isolated nucleic acid molecule (encoding $\sigma 1\beta$ receptor) comprising: a) nucleic acid molecule which hybridizes under stringent conditions to the nucleic acid molecule of SEQ ID NO:1 or degenerate variants thereof, b) vector comprising the nucleic acid of claim a and cell comprising said vector, c) method for producing a protein comprising the amino acid sequence of SEQ ID NO:2 or comprising fragments thereof.

The claims encompasses nucleic acid molecules encoding variants of the protein disclosed in SEQ ID NO:2, said variants may be completely unrelated, structurally and functionally to the protein encoded by SEQ ID NO:1 .

The common function of the nucleic acid (SEQ ID NO:1) encoding the polypeptide (SEQ ID NO:2), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The claims, as written, encompass nucleic acid encoding polypeptides which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotide encoding full-length

proteins, comprising fragments of SEQ ID NO:1 or variants encoding polypeptides classified as $\sigma 1\beta$ receptor, chimeric constructs, fusion constructs, variants and polynucleotides which hybridize to the nucleic acid of SEQ ID NO:1, which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:2. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. For example, what regions and fragments of the claimed $\sigma 1\beta$ receptor contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the

polynucleotides encompassed. No identifying characteristic or property of the instant polypnucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, **there is no clear evidence of activity possessed by the claimed genus of nucleic acid molecules encoding variant $\sigma 1\beta$ receptor polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function.** Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants $\sigma 1\beta$ receptor have the same activity as the protein disclosed in SEQ ID NO:2, since no activity is disclosed, or if they contain

the domain(s) of SEQ ID NO:2, containing the critical special technical feature of the claimed TMP, since no critical special technical feature is disclosed.

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of $\sigma 1\beta$ receptor, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the fragments and variants of claimed $\sigma 1\beta$ receptor relates to function. Similarly pertaining to nucleic acids which hybridize to the polynucleotide of SEQ ID NO:1, under unclearly defined hybridization conditions, what is the special technical feature encompassed by said nucleic acids and how do they relate to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:2 and 1, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids . There is no description of the conserved regions

which are critical to the structure and function of the genus claimed. The claimed nucleic acid encodes an orphan $\sigma 1\beta$ receptor whose activity has not been disclosed. The complexity of assigning a function and membership into a the genus of $\sigma 1$ receptors is highlighted by the diverse function/compound specificity of $\sigma 1\beta$ receptors disclosed above (IDS). Neither the claims nor the specification disclose what specific biological activity is associated with the claimed $\sigma 1\beta$ receptor or the special technical feature encompassed by specific domains associated with a specific activity of the claimed genus. The superfamily of $\sigma 1$ receptor are specialized proteins designed for chemical recognition of ligands, and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. $\sigma 1$ receptor interact with many diverse compounds having diverse effects. The important features which would help to define the $\sigma 1\beta$ receptor activity and define the genus claimed have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function. Similarly, pertaining to nucleic acids which hybridize to the polynucleotide of SEQ ID NO:1, under unclearly defined hybridization conditions, what is the special technical feature encompassed by said nucleic acids and how do they relate to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein of SEQ ID NO:2. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and

function of the genus claimed. Further vector comprising the claimed nucleic acid, cell comprising said vector, and method of producing polypeptide encoded by claimed nucleic are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 703-308-9435. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Nirmal S. Basi
Art Unit 1646
13/15/03

Michael D. Pak
MICHAEL PAK
PRIMARY EXAMINER